REMARKS

I. Status Summary

Claims 1-6, 8-13 and 30-32 are pending in the present application and are presently examined. The U.S. Patent and Trademark Office (hereinafter "the Patent Office") has rejected claims 1-6, 8-13 and 30-32.

Claim 30 is rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claim fails to satisfy the enablement requirement.

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pietu et al. (*Genome Research*, Vol. 6, pp. 492-503, 2000; hereinafter "Pietu et al.").

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. (*Mol. Cell Biol.*, Vol. 20, No. 21, pp. 8157-67, November 2000; hereinafter "Jelinsky et al.") in view of U.S. Patent Application Publication No. 2007/0037144 to Wohlgemuth et al. (hereinafter "Wohlgemuth et al.").

Claims 8-13 and 31-32 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. in view of Wohlgemuth et al. in further view of U.S. Patent No. 5,830,645 to Pinkel et al. (hereinafter "Pinkel et al.").

Claims 31 and 32 have been canceled without prejudice. Claims 1, 8 and 30 have been amended. Support for these amendments can be found throughout the claims and specification as filed, and in particular at page 1, lines 15-25; page 2, lines 1-8; page 3, lines 21-25; page 4, lines 1-9; page 7, lines 4-8, and lines 23-27; page 17, lines 17-31; in Figures 1 and 2; throughout the Examples; and in original claims 1, 2, 3, 8 and 30. Accordingly, no impermissible new matter has been added by this claim amendment.

Reconsideration of the application based on the amendments and arguments set forth herein is respectfully requested.

II. Interview Summary

Applicants conducted a Telephonic Interview with Examiner Karlheinz Skowronek on June 29, 2009. Applicants subsequently conducted Telephonic Interviews with Examiner Skowronek and Examiner Marjorie Moran on July 28, 2009, and August 21, 2009. Participating in the Telephonic Interviews with Examiners Skowronek and Moran were applicants' counsel of record, Arles A. Taylor, Jr., and Leon R. Legleiter. Applicants sincerely appreciate the Examiners' time and consideration in agreeing to and participating in the Telephonic Interview.

During the Telephonic Interviews, the nature of the disclosed and claimed subject matter was discussed. The outstanding rejections of claim 30 under 35 U.S.C. § 112, first paragraph; claims 1-4 under 35 U.S.C. § 102(b) over Pietu et al.; claims 1-6 under 35 U.S.C. § 103(a) over Jelinsky et al. and Wohlgemuth et al.; and claims 8-13 and 31-32 under 35 U.S.C. § 103(a) over Jelinsky et al., Wohlgemuth et al. and Pinkel et al. were discussed. Proposed claim amendments were also discussed. Upon discussing the nature of the disclosed and claimed subject matter and the proposed claim amendments, Examiners Skowronek and Moran agreed that claim 30 was enabled and claims 1-4 were distinguished from Pietu et al. Examiners Skowronek and Moran also indicated that they appreciated the distinctions between the claims with proposed claim amendments and the art cited in the § 103(a) rejections and suggested that the claims be amended to clarify the distinctions. Applicants respectfully submit that the Amendments and Remarks presented herein are believed to be consistent with their understanding of Examiner Skowronek's and Examiner Moran's position as presented during the Telephonic Interviews.

III. Response to the Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 30 is rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claim fails to satisfy the enablement requirement. The Patent Office contends that the description does not provide detailed guidance for calculating gene expression from genomic DNA hybridization array data. The Patent

Office contends that the predictability of calculating gene expression only from genomic DNA hybridized to arrays is unknown in the prior art. As such, the Patent Office contends that an unpredictable amount of experimentation would be required to practice the claimed invention.

After careful consideration of the rejections and the Patent Office's bases therefore, applicants respectfully traverse the rejections and submit the following remarks.

Initially, applicants respectfully submit that claim 30 has been amended herein to further clarify the claimed subject matter. In particular, claim 30 has been amended to recite, *inter alia*, "...calculating the expression level for a gene using the calculated weighing factor to determine the expression value v according to the formula: $v = 1/m \sum_{i=1}^{m} w_i S_i^{corrected}$ where *m* is the number of the oligo probes used to detect the expression level of the gene and $S_i^{corrected}$ is the corrected signal based on the calculated correction coefficient." Support for these amendments can be found throughout the claims and specification as filed, and in particular at page 7, lines 23-27; in Figure 2; and in original claim 30. Accordingly, no impermissible new matter has been added by this claim amendment.

As discussed in the Telephonic Interview of June 29, 2009, the genomic DNA hybridization signals are used for the calculation of the correction factors, e.g. correction coefficients, for each oligonucleotide probe. If a probe is subsequently employed in a microarray analysis, e.g. a cDNA microarray assay, each microarray signal indicative of gene expression can then be corrected using each individual probe's predetermined correction factor. As such, in contrast to the assertion by the Patent Office and as would be appreciated by one of ordinary skill in the art upon review of the instant disclosure, the genomic DNA is not used solely for calculating gene expression. Thus, the assertion upon which the instant enablement rejection is based appears to be unfounded.

Consequently, it is respectfully submitted that the rejection of claim 30 under 35 U.S.C. §112, first paragraph, has been addressed. It is therefore respectfully requested that the rejection of claim 30 under 35 U.S.C. §112, first paragraph, be withdrawn. A Notice of Allowance is also respectfully requested.

IV. Response to the Rejections Under 35 U.S.C. § 102(b)

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pietu et al. The Patent Office contends that Pietu et al. teaches each and every element of the rejected claims. Applicants respectfully traverse the rejections under § 102(b).

After careful consideration of the rejections and the Patent Office's bases therefore, applicants respectfully traverse the rejections and submit the following remarks.

Initially, without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 1 has been amended herein to further clarify the claimed subject matter. In particular, claim 1 has been amended to recite a step of deriving a correction coefficient for each oligo probe using genomic DNA hybridizations to a first microarray and a step of correcting oligo probe hybridization signals from a second microarray for gene expression by employing the correction coefficients. Furthermore, claim 1 has been amended to clarify the calculation of the correction coefficient for each oligo probe according to the equation $C_i = 1/S_i$, where C_i is the correction coefficient and S_i is the average of the signals observed in the genomic DNA hybridizations. Support for these amendments can be found throughout the claims and specification as filed, and in particular at page 1, lines 15-25; page 2, lines 1-8; page 3, lines 21-25; page 4, lines 1-9; page 7, lines 4-8; page 17, lines 17-31; in Figure 1; throughout the Examples; and in original claims 1, 2, 3, 8 and 30. Accordingly, no impermissible new matter has been added by this claim amendment.

Applicants respectfully submit that Pietu et al. fails to teach a method of calculating a correction coefficient for each oligo probe by deriving a correction coefficient for each oligo probe using genomic DNA hybridizations from a first microarray and then employing the correction coefficients in a second microarray for gene expression, as presently claimed. Rather, Pietu et al. is, at best, directed to normalizing the signal intensities obtained from a microarray hybridization and makes no mention of calculating correction coefficients for the probes themselves.

In the Interview Summary of July 1, 2009, the Patent Office refers to p. 495, column 2, of Pietu et al. in alleging that the reference teaches the use of genomic DNA. However, while Pietu et al. does mention genomic DNA probes, it is believed to be in the context of detecting clones harboring repetitive sequences, not for deriving a correction coefficient for each oligo probe as presently claimed. As such, when read as a whole, it is believed that Pietu et al. does not teach deriving a correction coefficient for each oligo probe using genomic DNA hybridizations, as presently claimed.

Further, at page 502, column 1, Pietu et al. describes the hybridization signal analysis as follows:

> Different types of values are obtained for the quantitation of the dot intensity: the radius of the dot, the mean of the dot pixel intensities for one dot, the maximal intensity of the pixels of the dot, the sum of the pixel intensities of the dot, the average of the pixel intensities of the dot weighted by the distance to the center of the dot. We have chosen to use the mean of the pixel intensities for each dot or intensity mean, noted as Im. To take into account experimental variations in specific activity of the cDNA probe preparations or exposure time that might alter the signal intensity, the data obtained from different hybridizations were normalized by dividing the Im for each dot by the average of the intensities of all the dots present on the filter to get a normalized Im value (nIm).

(emphasis added). Noticeably absent is any mention of deriving a correction coefficient for each oligo probe using genomic DNA hybridizations in a first microarray and employing those correction coefficients in determining gene expression in a second microarray. In marked contrast, the method of Pietu et al., at

best, normalizes the signal intensities obtained from the microarray hybridization for gene expression by averaging the intensities of all the dots present on the filter. Thus, the method of Pietu et al. is believed to suffer from particular deficiencies overcome by the presently disclosed and claimed subject matter. *See*, e.g., page 1, lines 15-33; and page 11, lines, 10-12, of the instant specification. Therefore, it is believed that Pietu et al. does not disclose each and every element of the present claims.

Accordingly, applicants respectfully submit that Pietu et al. fails to anticipate each and every element of present claim 1, or claims 2-4 depending therefrom. It is therefore respectfully requested that Pietu et al. as a reference be withdrawn, and hence, that the rejection of claims 1-4 under 35 U.S.C. §102(b) be withdrawn. A Notice of Allowance is also respectfully requested.

V. Response to the Rejections Under 35 U.S.C. § 103(a)

V.A. Rejection of Claims 1-6 Over Jelinsky et al. and Wohlgemuth et al.

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. (*Mol. Cell Biol.*, Vol. 20, No. 21, pp. 8157-67, November 2000; hereinafter "Jelinsky et al.") in view of U.S. Patent Application Publication No. 2007/0037144 to Wohlgemuth et al. (hereinafter "Wohlgemuth et al."). The Patent Office admits that Jelinsky et al. fails to teach the individual calculation of correction coefficients for individual probes where the average signal of the individual probes is made to equal a constant. However, the Patent Office contends that Wohlgemuth et al. compensates for this deficiency in Jelinsky et al.

After careful consideration of the rejections and the Patent Office's bases therefore, applicants respectfully traverse the rejections and submit the following remarks.

Initially, without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 1 has been amended as discussed hereinabove. Present claim 1 recites a step of deriving a correction coefficient for each oligo probe

using genomic DNA hybridizations to a first microarray and a step of correcting oligo probe hybridization signals from a second microarray for gene expression by employing the correction coefficients.

Neither Jelinsky et al. nor Wohlgemuth et al., alone or in combination, teach a method of calculating a correction coefficient for each oligo probe by deriving a correction coefficient for each oligo probe using genomic DNA hybridizations from a first microarray and then employing the correction coefficients in a second microarray for gene expression, as presently claimed. The Patent Office, at page 9 of the Official Action, admits that Jelinsky et al. fails to teach the first step of deriving a correction coefficient for each oligo probe using genomic DNA hybridizations, but contends that Wohlgemuth et al. compensates for the deficiency. Applicants respectfully disagree.

Wohlgemuth et al., at best, appears to correct probe signals for background noise for purposes of selecting expression data for analysis. *See*, paragraph [0207] of Wohlgemuth et al. The Patent Office contends that Wohlgemuth et al., at paragraph [0207], teaches that an average and standard deviation for the signals observed for each probe are calculated. However, applicants respectfully submit that paragraph [0207] refers to correcting the intensity of signals acquired from microarray analysis employed for gene expression. Thus, as the heading above paragraph [0207] suggests, the normalization procedure discussed in paragraphs [0207]-[0217] pertains to the analysis of gene expression profile data, not deriving a correction coefficient for each oligo probe using genomic DNA. Stated another way, at paragraphs [0207]-[0217] of Wohlgemuth et al., the gene expression microarray has already been completed without ever having derived a correction coefficient for each oligo probe using genomic DNA hybridizations (step (a) in claim 1). Thus, applicants respectfully submit that Wohlgemuth et al. fails to teach a method of calculating a correction coefficient for each oligo probe by deriving a correction coefficient for each oligo probe using genomic DNA hybridizations from a first microarray and then

employing the correction coefficients in a second microarray for gene expression, as presently claimed.

Furthermore, the alleged scaling of the data in paragraph [0212] is not believed to be tantamount to correcting oligo probe hybridization signals, comprising calculating a correction coefficient for each oligo probe, as recited in claim 1. In particular, the scaling referenced in paragraph [0212] is not believed to be based upon individual probe correction coefficients, but rather, the median, the mean, the trimmed mean, or percentile of the entire dataset. Further, in contrast to the Patent Office's assertion, paragraph [0214] is not believed to teach the use of a scaling factor for the correction of each individual probe as presently claimed. Rather, paragraph [0214] is at best believed to be directed to correcting for inter-assay variation such that expression levels can be compared between different hybridization experiments. This is not believed to be tantamount to deriving a correction coefficient for each oligo probe using genomic DNA hybridization.

Finally, the Patent Office refers to paragraph [0091] of Wohlgemuth et al. to support the contention that Wohlgemuth et al. teach DNA that is genomic DNA. Indeed, Wohlgemuth et al. mentions genomic DNA at paragraph [0091]. However, when read in context, there is no teaching or suggestion that Wohlgemuth et al. employs this genomic DNA in a hybridization from which correction coefficients for each oligo probe are calculated. The Patent Office further contends that there is a direct suggestion that the genomic DNA may be used in the process disclosed in paragraphs [0207]-[0217]. Applicants respectfully submit that even assuming *arguendo* that genomic DNA is used in the process disclosed in paragraphs [0207]-[0217], this process is directed to the analysis of gene expression profile data, not deriving a correction coefficient for each oligo probe using genomic DNA. Thus, applicants maintain that there is no teaching or suggestion that Wohlgemuth et al. employs genomic DNA in a hybridization from which correction coefficients for each oligo probe are calculated.

Thus, applicants respectfully submit that Wohlgemuth et al. fails to compensate for the admitted deficiency in Jelinsky et al. Therefore, applicants respectfully submit that the proposed combination of Jelinsky et al. and Wohlgemuth et al. fails to teach or suggest each and every element of claim 1. Given that claims 2-6 depend either directly or indirectly from claim 1, they too are believed to be distinguished from the cited references.

Consequently, it is respectfully sbmitted that the rejection of claims 1-6 under 35 U.S.C. §103(a) as being obvious over Jelinsky et al. in view of Wohlgemuth et al. has been addressed. It is therefore respectfully requested that the rejection of claims 1-6 under 35 U.S.C. §103(a) be withdrawn. A Notice of Allowance is also respectfully requested.

V.B. Rejection of Claims 8-13 Over Jelinsky et al., Wohlgemuth et al. and Pinkel et al.

Claims 8-13 and 31-32 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Jelinsky et al. in view of Wohlgemuth et al. in further view of U.S. Patent No. 5,830,645 to Pinkel et al. (hereinafter "Pinkel et al."). Applicants respectfully traverse the rejections under § 103(a).

After careful consideration of the rejections and the Patent Office's bases therefore, applicants respectfully traverse the rejections and submit the following remarks.

Preliminarily, applicants respectfully submit that claims 31 and 32 have been canceled without prejudice. Accordingly, applicants respectfully submit that the instant rejection is believed to be moot with respect to claims 31 and 32.

Furthermore, without acquiescing to the contentions of the Patent Office, applicants respectfully submit that claim 8 has been amended herein to further clarify the claimed subject matter. In particular, claim 8 has been amended to recite a method of obtaining correction coefficients for probes, the method comprising, *inter alia*, determining a dynamic range for genomic DNA binding by measuring a concentration signal curve; and measuring signals from each probe during multiple

hybridizations to a microarray with the genomic DNA within a linear range, wherein the linear range is based on the determination of the dynamic range. Furthermore, similar to claim 1, claim 8 has been amended to clarify the calculation of the correction coefficient. Support for these amendments can be found throughout the claims and specification as filed, and in particular at page 1, lines 15-25; page 2, lines 1-8; page 3, lines 21-25; page 4, lines 1-9; page 7, lines 4-8; page 17, lines 17-31; in Figure 1; throughout the Examples; and in original claims 1, 2, 3, 8 and 30. Accordingly, no impermissible new matter has been added by this claim amendment.

Applicants respectfully submit that Jelinsky et al., Wohlgemuth et al. and Pinkel et al., alone or in combination, fail to teach or suggest the elements of present claim 1. In particular, applicants respectfully submit that the proposed combination fails to teach or suggest a method of obtaining correction coefficients for probes, the method comprising, *inter alia*, determining a dynamic range for genomic DNA binding by measuring a concentration signal curve; measuring signals from each probe during multiple hybridizations to a microarray with the genomic DNA within a linear range, wherein the linear range is based on the determination of the dynamic range; and calculating a correction coefficient for each probe based on the measured signals from the genomic DNA hybridizations according to the equation $C_i = 1/S_i$, where C_i is the correction coefficient and S_i is the average signal for each probe from the normalized signal intensities.

Moreover, applicants respectfully submit that the Pinkel et al. is directed to comparative genomic hybridization (CGH), an approach to detect the presence and identify the location of chromosal abnormalities. Applicants respectfully submit that CGH is distinct from microarray analysis for gene expression, and particularly a method of correcting oligo probe hybridization signals as presently claimed. Indeed, Pinkel et al. distinguishes CGH from microarray hybridization for gene expression analysis using probes for specific genes. *See*, e.g., column 1, line 50, through column 2, line 28 of Pinkel et al. As such, given the distinction between the type of analysis performed in Pinkel et al. and that of the presently disclosed and claimed

subject matter, applicants respectfully submit that Pinkel et al. is believed to be inapplicable to the present claims. Further, given this distinction, it is believed that one of ordinary skill in the art would be dissuaded from combining the teachings of Pinkel et al. with that of Jelinsky et al. and Wohlgemuth et al. to arrive at the presently disclosed and claimed subject matter.

Taken together, applicants respectfully submit that Jelinsky et al., Wohlgemuth et al. and Pinkel et al., alone or in combination, fail to support a rejection of claim 8 under 35 U.S.C. §103(a). Given that claims 9-13 depend either directly or indirectly from claim 8, they too are believed to be distinguished from the cited references.

Consequently, it is respectfully submitted that the rejection of claims 8-13 under 35 U.S.C. §103(a) as being obvious over Jelinsky et al. in view of Wohlgemuth et al. and further in view of Pinkel et al. has been addressed. It is therefore respectfully requested that the rejection of claims 8-13 under 35 U.S.C. §103(a) be withdrawn. A Notice of Allowance is also respectfully requested.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any additional fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
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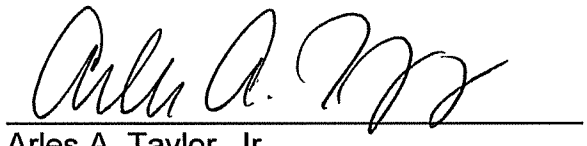
Date: 09/11/2009

By: 

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